AD-A011 872

AEROSOL PARTICLE SIZE AS A FACTOR IN PULMONARY TOXICITY

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Prepared for:

National Institute of Environmental Health Sciences
Atomic Energy Commission

December 1974

AD A011872

197073

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1 REPORT NUMBER [redacted] Paper No. 23

2 GOVT ACCESSION NO

3 RECIPIENT'S CATALOG NUMBER

4 TITLE (and Subtitle)
AEROSOL PARTICLE SIZE AS A FACTOR IN PULMONARY TOXICITY

5 TYPE OF REPORT & PERIOD COVERED
Final Report

6 PERFORMING ORG. REPORT NUMBER

7 AUTHOR(s)
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8 CONTRACT OR GRANT NUMBER(s)
In part under Contract F33615-73-C-4059*

9 PERFORMING ORGANIZATION NAME AND ADDRESS
Aerospace Medical Research Laboratory, Aerospace Medical Division, Air Force Systems Command, Wright-Patterson Air Force Base, Ohio 45433

10 PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
62202F; 6302; 630201; 63020113

11 CONTROLLING OFFICE NAME AND ADDRESS
Aerospace Medical Research Laboratory, Aerospace Medical Division, Air Force Systems Command, Wright-Patterson Air Force Base, Ohio 45433

12 REPORT DATE
December 1974

13 NUMBER OF PAGES
15

14 MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)

15 SECURITY CLASS. (of this report)
Unclassified

15a DECLASSIFICATION/DOWNGRADING SCHEDULE

16 DISTRIBUTION STATEMENT (of this Report)

Approved for public release; distribution unlimited.

17 DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18 SUPPLEMENTARY NOTES

*Conference was arranged by the Toxic Hazards Research Unit of the University of California, Irvine

19 KEY WORDS (Continue on reverse side if necessary and identify by block number)

Subject Field: 0620; 0615; 0606
Inhalation toxicology
Environmental toxicology
Environmental Carciogenesis
Pathology
Cellular toxicology

20 ABSTRACT (Continue on reverse side if necessary and identify by block number)

Major technical areas discussed included ecosystem modeling, water pollution, water reuse, toxic hazards evaluation of fire extinguishants, environmental carcinogenesis, and cellular toxicology.

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

AMRL-TR-74-125

PAPER NO. 23

AEROSOL PARTICLE SIZE AS A FACTOR IN PULMONARY TOXICITY*

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"Indeed, for a given magnitude of atmospheric exposure to a potentially toxic particulate contaminant, the resulting hazard can range all the way from an insignificant level to one of great danger, depending upon the size of the inhaled particles and other factors that determine their fate in the respiratory system."
Theodore Hatch and Paul Gross from the introduction in Pulmonary Deposition and Retention of Inhaled Aerosols, Academic Press, N. Y. 1974, pg. 2.

INTRODUCTION

The respiratory tract is both a portal of entry and a target for environmental air pollutants. In an industrial society vast numbers of people are exposed occupationally and more generally, environmentally, to a variety of dusts, fumes and other aerosols which may produce lung disease. Particulate toxic agents include asbestos, silica, metal fumes, infectious agents, acid mists, fibrous glass, and in the nuclear industry, radioactive aerosols. Important considerations in assessing inhalation hazards include the biological status of the exposed individual and the chemical and physical characteristics of the aerosol. Factors related to particle size that influence the toxicity of inhaled aerosols in humans include mass per particle, aerodynamic behavior, rate of dissolution in the lung, efficiency of uptake by macrophages, and the ability of particles to penetrate biological membranes.

*Research supported by the National Institute of Environmental Health Sciences (NIEHS) via AEC Contract AT (29-2)-1013 with Lovelace Foundation.

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AEROSOLS

An aerosol is a relatively stable suspension of small, solid particles or liquid droplets in a gas. Only a smooth, spherical particle or droplet can be conveniently described by a unique geometric diameter. Since aerosols of solids rarely consist of smooth, spherical particles, conventions for particle diameters are defined which are usually based upon available measurement techniques. For example, the size of a particle may be described in terms of its projected area diameter, some defined as the geometric diameter of a circle which has the same area as the two-dimensional outline of the particle lying on a collection surface. Other conventions for describing physical size can be based on measurements of scattered light, surface area, electrical mobility or other physical or chemical phenomena. Methods for physical sizing of aerosols have been discussed by Raabe (1970) and by Mercer (1973).

Because important inertial properties of particles, such as settling speed or ability to turn corners in a moving air stream, depend on factors such as density and shape in addition to physical size, it is often useful to describe particles in terms of an aerodynamic (equivalent) diameter. The aerodynamic (equivalent) diameter which is usually used in inhalation toxicology is the geometric diameter of a spherical particle of unit density material (ρ = 1 gm/cm^3) which has the same settling velocity (in still air) as the particle being described. Two particles having markedly different densities or shapes may vary considerably in physical diameter but have the same aerodynamic diameter.

For particles larger than about 0.5 micrometer (μm) in physical diameter where inertial and gravitational forces dominate particle motion, the aerodynamic diameter can be used to predict particle deposition in the respiratory tract. Below about 0.5 μm the particle size is approaching the mean-free-path between collisions of air molecules, and diffusional forces tend to dominate the particle motion and the physical diameter of the particle correlates more closely with aerodynamic behavior, and should be used when considering particle motion.

Since individual particles in a given aerosol usually vary widely in size, statistical descriptions are often used to describe aerosols. For example, aerosol size distributions may be described by a mean physical or aerodynamic diameter and the associated standard deviation (or by a median diameter and geometric standard deviation).

INHALED PARTICLE DEPOSITION AND CLEARANCE

Inhaled particles may deposit on the various surfaces of the respiratory tract. The Task Group on Lung Dynamics of the International Commission on Radiological Protection has proposed a general model useful in estimating the potential hazards associated with inhaled aerosols (Task Group on Lung Dynamics, 1966). This model includes estimates of both the fractional deposition of inhaled particles with respect to aerodynamic size, and clearance of deposited particles from the respiratory tract with respect to deposition region and basic particle properties. The model divides the respiratory tract into three regions based upon anatomical features and particle deposition and clearance phenomena. The regions, called (a) the nasopharynx (NP), (b) the tracheobronchial region (TB) and (c) the pulmonary or parenchymal region (P), are referred to in Figure 1.

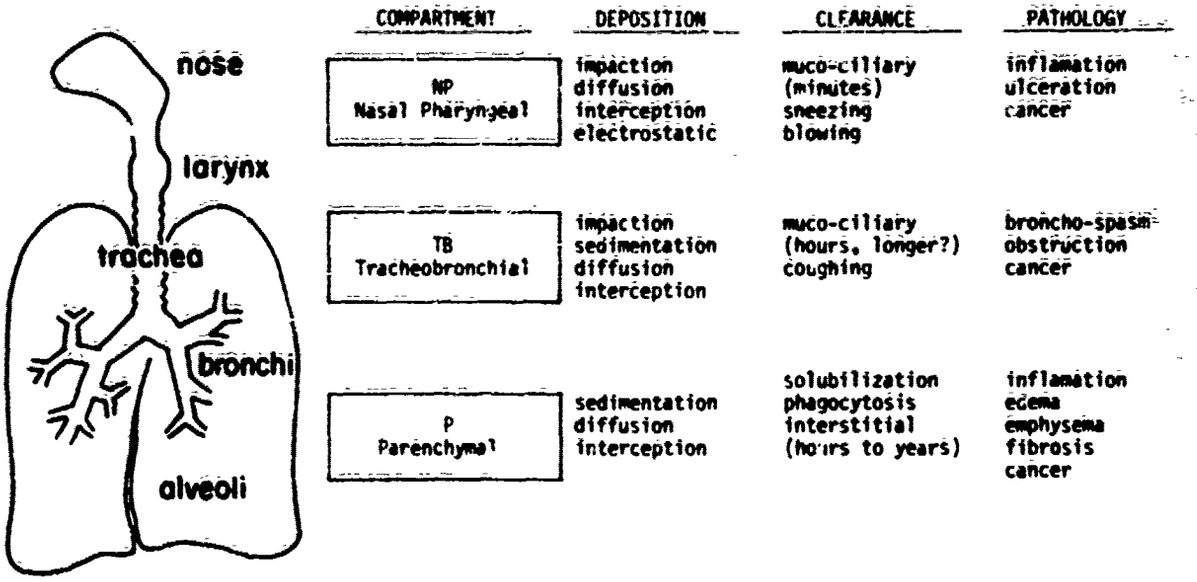

Figure 1. Compartmental model of the respiratory tract as used by the Task Group on Lung Dynamics of the ICRP (1966) with the airways from nose to larynx in the NP (nasopharyngeal) region, the trachea and ciliated bronchi and bronchioles in the (tracheobronchial) region and the nonciliated bronchioles, alveolar ducts, alveolar sacs, atria and alveoli in the P (parenchymal or pulmonary) region. The types of particle deposition, clearance and potential pathology are summarized for each.

The nasopharynx (NP) begins at the anterior nares and includes the respiratory airway down to the level of the larynx. Particle deposition in this region is primarily limited to the larger particles whose inertial properties cause impaction in the nasal passages or entrapment by nasal hairs. Two pathways, both having a half-time of 4 minutes, are used by the Task Group to describe the clearance of particles which deposit in the NP compartment. The first describes uptake of relatively soluble material into the blood, while the second represents physical clearance by muco-ciliary transport to the throat for subsequent swallowing.

Experimental data indicate that the anterior one-third of the nose, where 80% of 7 μm particles deposit, does not clear except by blowing, wiping or other extrinsic means (Walsh, 1970: Proctor, 1971) and effective removal of insoluble particles may require one to two days. The posterior portions of the nose have mucociliary clearance, with clearance half-times of about 6-7 hour (Morrow, 1972).

The tracheobronchial region (TB) begins at the larynx and includes the trachea and the ciliated bronchial airways down to and including the terminal bronchioles. A relatively small fraction of all sizes of particles which pass through the NP region will deposit in the tracheobronchial region. The mechanisms of inertial impaction at bifurcations, sedimentation and, for small particles, Brownian diffusion cause TB deposition. Interception can be an important deposition mechanism for fibrous dusts. In mouth breathing of aerosols, such as in cigarette smoking, the benefits of the collection of larger particles in the nose are lost and these larger particles tend to deposit in the TB region with high efficiency. An important characteristic of the TB region in the Task Group model is that this region is both ciliated and equipped with mucous secreting elements so that clearance of deposited particles rapidly occurs by muco-ciliary action to the throat for swallowing. Again, relatively soluble material may enter the systemic circulation.

The rate of mucous movement is slowest in the finer airways and increases toward the trachea. Since particles depositing in the tracheobronchial tree are probably distributed differently with respect to size, with smaller particles tending to deposit deeper in the lung, one expects larger particles to clear more quickly. Clearance of material in the TB compartment cannot be described by a single rate. TB clearance half-times from experimental studies imply that the larger airways, intermediate airways and finer airways clear with halftimes of about 0.5 hours, 2.5 hours and 5 hours, respectively (Morrow, et al., 1967; Morrow, 1972). It is relatively certain that material with slow dissolution rates in the TB compartment will not persist for longer than about 24 hours in healthy humans. The detailed nature of the mucociliary clearance mechanism has been recently reviewed by Schlesinger (1973).

The third compartment, the pulmonary or parenchymal region (P) represents the functional gas exchange sites of the lung. It includes respiratory bronchioles, alveolar ducts, alveolar sacs, atria, and alveoli. For particles to reach and depos. in this region they must penetrate the NP and TB regions on inspiration and either by settling or diffusion come into contact with pulmonary surfaces. Since a portion of each breath remains unexhaled, the times available for deposition may be long for some particles. Smaller particles are of primary importance in pulmonary deposition. Clearance from the pulmonary region is not completely understood, but the Task Group suggests several mechanisms including: (a) the dissolution of relatively soluble material with absorption into the systemic circulation, (b) direct passage of particles into the blood, (c) phagocytosis of particles by macrophages with translocation to the ciliated airways and, (d) transfer of particles to the lymphatic system including lymph nodes.

The fate of particles deposited in the P compartment is strongly dependent on the mechanical stability of the particles. Particles that undergo significant dissolution in the fluids found in the lung may dissolve while still within the air spaces, inside phagocytes or while in interstitial spaces. The Task Group (1966) recommended the use of three clearance half-times of 30 minutes, 90 days and 360 days for readily, intermediately and minimally soluble materials, respectively. An omitted factor in this clearance model is particle size (the rate of dissolution of a material in biological fluids being dependent on the available surface area of particles). At the present time clearance rates for the deep lung for humans are not known for many materials and the rates recommended by the Task Group provide a useful guide in the absence of detailed information.

The relative deposition of inhaled particles of various aerodynamic diameters as suggested by the Task Group for a moderate level of respiratory effort is shown in Figure 2. The total deposition and the fractional deposition in individual compartments are shown. The minimum total deposition at about 0.5 μm occurs since particles of this size are not strongly influenced by either inertial or diffusional forces.

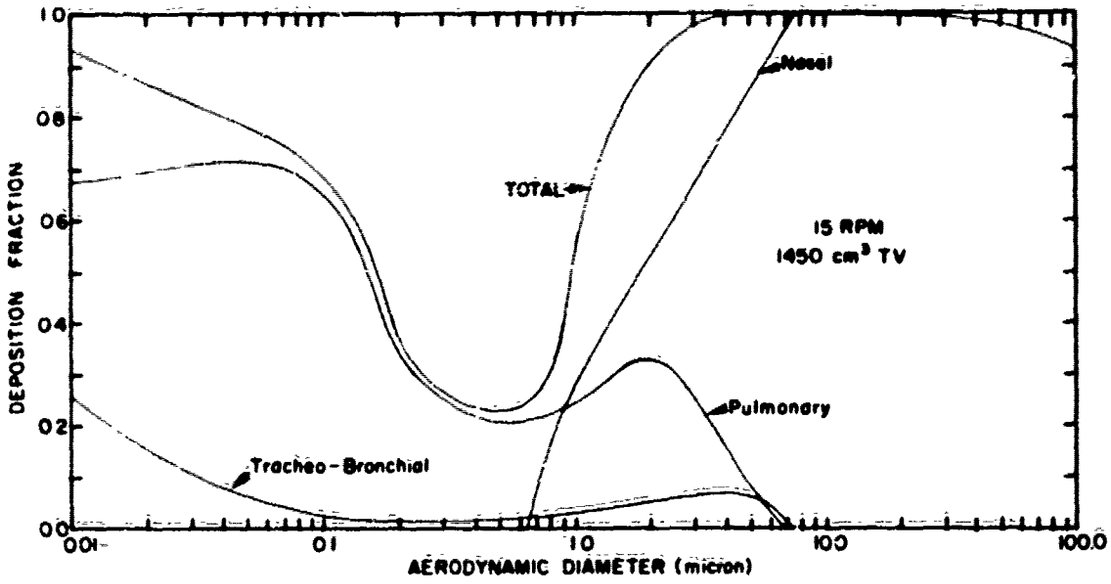

Figure 2. The deposition fraction of inhaled aerosols of various individual particle sizes with respect to aerodynamic diameter (μm) in the modeled regions of the human respiratory tract (assuming a respiratory rate of 15 per minute and a tidal volume of 1450 cm^3) as recommended by the Task Group on Lung Dynamics of the ICRP (1966).

TOXICITY AND PARTICLE SIZE

Particle size influences the toxicity of inhaled aerosols for a variety of reasons: (a) particle size affects the mass per particle and might therefore be expected to affect potential for hazard: (b) as described, the site of deposition within the respiratory tract as well as the clearance pattern is, to a great extent, influenced by aerodynamic size; (c) smaller particles have larger surface-to-mass ratios and therefore are more active with respect to chemical or physical interaction and rate of dissolution: (d) rate of phagocytic uptake may vary with particle size; and (e) particle size may influence the penetration of particles through membranes of the lung.

(a) Particle Mass

The total mass of material deposited in the respiratory tract is usually important in determining the potential toxicity for an inhaled aerosol. Hence, the deposition of a few particles that have a large mass

per particle may be more important than the deposition of numerous particles that are each small in mass. This fact is particularly relevant because the mass per particle for aerosols in the respirable size range can vary over many orders of magnitude. For example, since the mass of a spherical particle is proportional to the cube of the geometric diameter, 1000 particles of 0.1 μm diameter must be deposited in the lung to equal the mass burden from the deposition of but a single 1 μm diameter particle.

When particles of different individual masses are deposited in the respiratory tract, the number of cells which each directly affects may vary significantly with respect to mass per particle (depending upon the mechanism and range of influence). A given amount of mass deposited in the respiratory tract may be distributed among numerous small particles or among few large particles and the effect on overall toxicity of these different situations may not be readily apparent. These considerations are probably less important for rapidly dissolved material that is in the particulate state only a brief time, and most important for material that is resistant to dissolution in the lung.

The case of relatively insoluble radioactive particles of alpha emitting materials deposited in the pulmonary region provides a timely example. Since the major direct effect of the particles on the surrounding cells relates to the alpha emissions, each aerosol particle irradiates a small surrounding volume of the lung. It can be argued that a given mass burden in the lung distributed among a few massive particles is less carcinogenic because the number of cells at risk is limited and those that are irradiated may in fact be over-irradiated and in effect sterilized, preventing development of neoplasia. On the other hand, it can also be argued that the distribution of the lung burden in larger particles is more hazardous because of the large local radiation doses received by cells surrounding the particles, and it is less hazardous to have smaller radiation doses which are associated with smaller particles (even though more cells are irradiated). This so-called "hot particle" question bears on the environmental impact of a nuclear technology and is currently being studied by many investigators.

(b) Aerodynamic Properties

Types of solid particles that can be identified with respect to their shape and concomitant aerodynamic character include: relatively globular particles that tend to approximate spherical shapes; plate-like or flat particles; long, thin particles or fibers; and clusters or agglomerates of particles. For relatively spherical particles of a given aerodynamic diameter, higher density particles have lower total mass. Hollow, or spongy particles of a homogeneous material will therefore have more mass per particle for a given aerodynamic size. Differences in toxicity with respect to particle density have not been demonstrated.

Long, thin fibers have aerodynamic diameters nearly independent of their length up to a length-to-diameter ratio of about 20 (Timbrell, 1972; Mercer, 1973). For this reason asbestos fibers containing considerable mass can behave like smaller particles aerodynamically and penetrate deeply into the lung. This effect is emphasized by the many cases of pulmonary asbestosis from the asbestos industry.

A particularly interesting aerosol in industrial toxicology, the metal fume, consists of chain-like agglomerates of particles smaller than 0.1 μm (Figure 3). Extreme toxicity is known to be associated with the inhalation of metal fumes. This may be due to the relatively large surface area associated with a given mass of fume aerosol. The aerodynamic drag on the large surfaces of fume particles allows them to follow airstreams and escape impaction in the NP and TB compartments. As in the case of the asbestos fibers, the ability of metal fume particles to penetrate to the deep lung undoubtedly contributes to their hazard.

(c) Surface Area

Two categories of toxic particulate materials can be identified with respect to mechanism of toxicity. Materials such as asbestos and quartz that are hazardous as solid particles, appear to have toxic shape or surface characteristics. Pneumoconioses in general are caused by the presence of intact particles. Other materials like Pb and Mn probably require dissolution, or at least some form of transformation from the original particle, in order to be toxic (Hatch and Gross, 1964). For both categories of particulate materials the specific surface, or surface-to-mass ratio, affects their toxicity. The surface-to-mass ratio for smooth spherical particles is equal to $6/\rho D$, where ρ is the physical density and D the geometric diameter. One micrometer diameter unit density particles have a specific surface of 6 m^2 g, while 0.01 μm particles have an area of 600 m^2 g. The increased toxicity of finely divided silica, discussed by Hatch and Gross (1964), appears to relate to increased surface area. The mechanism for toxicity appears to involve a tissue reaction to the particle surface.

A model for dissolution of particles in the P compartment that correlates well with experimental data on deep lung clearance has been proposed by Mercer (1967). The model assumes a rate of dissolution that is proportional to the available surface area of the particles. For materials that are toxic when dissolved, increased surface area tends to enhance toxicity. The dissolution of silver particles (mass median diameter = 0.04 μm) in various aqueous media indicates that even a so-called "insoluble" material can undergo rapid dissolution when in a finely divided state (Figure 4).

Figure 3. Electron micrograph of a sample of a metal-fume aerosol. The small, spherical primary particles, silver in this case, cluster to form branched chain-like agglomerates. Such agglomerates have large surface-to-mass ratios, can remain suspended in air for long periods (due to viscous drag) and can undergo rapid dissolution in the body. From Phalen (1972).

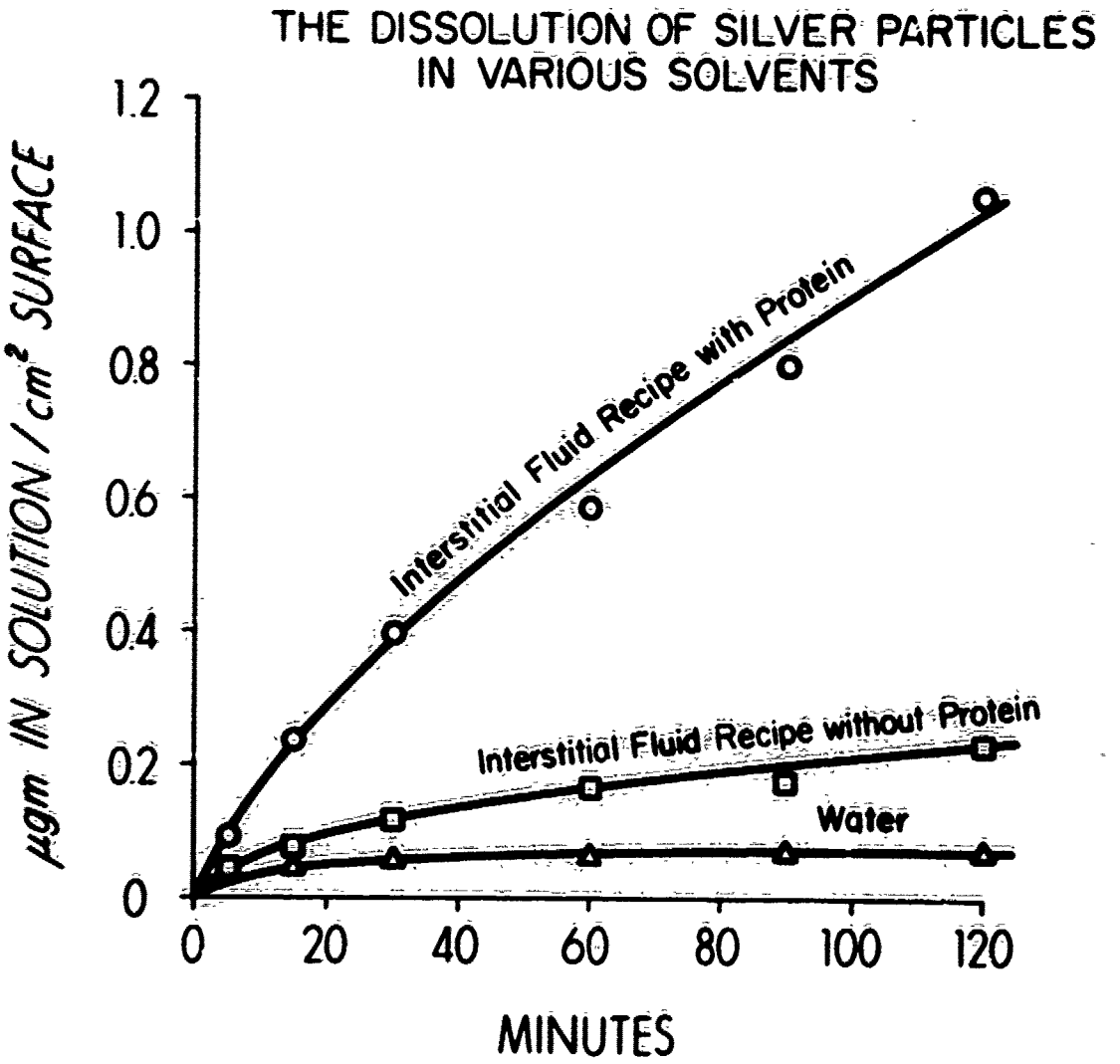

Figure 4. Dissolution of metallic silver particles (count median diameter = 0.03 µm) in various aqueous media given as µgm dissolved per cm² of particle surface for various times up to 120 minutes. Gamble's interstitial fluid recipe with and without protein (bovine albumin) and distilled water were used. The increased rate of dissolution with protein present is probably due to the binding of silver ions to proteins. The silver particles used in this study are shown in Figure 3. From Phalen (1972).

On the basis of the dissolution rate found in the protein containing fluid, Mercer's model predicts that these silver particles should essentially completely dissolve in the lung in about 48 hours (Phalen, 1972). Systemic toxicants can be expected to be more rapidly dissolved and hence more hazardous when deposited in the lung as small particles.

(d) Other Size Dependent Factors

Aside from the influence of particle size on magnitude and distribution of dose, deposition pattern and dissolution rate, there are other size-related factors that may bear on toxicity. An optimal particle size of 1.5 μm for efficient uptake of polystyrene spheres by macrophages was suggested by Holma (1967). Holma (1967) gave an upper limit of 8 μm diameter for phagocytic uptake. The question of relative efficiency of uptake by macrophages of the lung for particles in the respirable size range (about 0.01 to 10 μm) is worthy of further investigation.

The permeability of alveolar membranes to bare particles has been reported by Gross and Estrick (1954) and more recently by Tucker et al. (1973). In the earlier study rats were given small carbon particles (≤0.2 μm) by intratracheal injection. Nineteen hours later the particles were found extracellularly in interstitial spaces; considered by the authors to be proof of membrane penetration by bare particles. In Tucker's experiments carmine particles ranging from about 5 μm down to below 0.05 μm in diameter were inhaled by rats. At 3 hours post inhalation, microscopic examination revealed "small aggregates, up to cell size" in the extracellular interstitial spaces. Particulate material in the interstitium would presumably either remain, dissolve, undergo transport to lymphatic or blood vessels or return to the respiratory airway. The presence of interstitial foreign material for prolonged periods may lead to lung diseases. The role of particle size in membrane penetration is not yet well understood.

SUMMARY

The particle size distribution of inhaled aerosols is a factor in pulmonary toxicity for several reasons. Among those discussed are the relationship between particle size and amount of toxic agent per particle, the influence of aerodynamic and real size on the regional deposition within various anatomical regions of the respiratory tract and the effect of both deposition site and particle size per se on clearance kinetics. The role of particle size in the assessment of environmental hazards is one that is increasingly being realized as important.

ACKNOWLEDGEMENTS

The authors are indebted to Drs. R. K. Jones, R. G. Cuddihy and F. F. Hahn for beneficial advice in the preparation of this paper.

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